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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,176	02/06/2004	Miles William Carroll	021911000510	7186

20350 7590 10/12/2006

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,176	CARROLL ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/2/04, 2/6/04, 9/15/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-53* is/are pending in the application.

4a) Of the above claim(s) *34-36 and 42-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-41 and 49-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/13/04, 12/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to Comply with the Sequence Rules.

DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Full compliance with the sequence rules is required in response to this Office Action. A complete response to this Office Action should include both compliance with the sequence rules and a response to the Office Action set forth below. Failure to fully comply with both these requirements in the time period set forth in this Office Action will be held non-responsive.

2. Applicants are required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, page 56 at lines 6 and 7).

3. Applicant's amendments filed 8/2/04, 2/6/04 and 9/15/06 and Applicant's responses filed 3/22/06 and 6/5/06 are acknowledged and have been entered.

4. Applicant's election with traverse of Group I (newly added claims 43-53), and species of SEQ ID NO: 5 in responses filed 3/22/06 and 6/5/06 and in Applicant's amendment and response filed 9/15/06 is acknowledged.

Applicant's withdrawal of traversal between Groups I and II in Applicant's amendment and response filed 9/15/06 is acknowledged.

Applicant's traversal of the species requirement (of record in Applicant's response filed 3/22/06) has been fully considered, but is not persuasive.

It is the Examiner's position with regard to Applicant's argument (*i.e.*, that there has been no demonstration that more than a reasonable number of species is encompassed by the pending claims, that if no prior art is found to anticipate or render obvious the elected species, the search of the claims should be extended to the next species, and that the claims include the possible feature of both vectors encoding the same 5T4 antigen) that the species are modified 5T4 peptide antigens with different sequences that elicit differently restricted CTL responses, that MPEP 803.02 (revision 5, 8/06) indicates that the Office is not obligated to extend the search and examination to additional species when the elected or subsequent species is rejected under any of 35 USC 101, 102, 103 or 112, first paragraph, and the relevance of Applicant's last remark to the species traversal is not understood by the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 34-36 and 42-47(non-elected species of Group I) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 37-41 and 48-52 are currently being examined.

5. The disclosure is objected to because of the following informalities:

a. There are two sets of page numbers on each page of the specification and originally filed claims, *i.e.,* one at the top center and one at the bottom left.

b. There is no heading for the Brief Description of the Drawings.

c. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example on page 6 at lines 5-6, on page 28 at lines 5 and 11-12, on page 27 at line 25, on page 28 at lines 5 and 11, on page 30 at line 10, on page 31 at lines 2, 5 and 8. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

d. The use of the trademarks LIPOFECTIN, EUDRAGIT, AMPHIGEN AND ALHYDROGEL have been noted in this application on page 49 at line 23, page 42 at line 2, and page 41 at lines 4-5. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction(s) is/are required.

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

7. It is noted by the Examiner that Applicant has filed a cover letter for an IDS on 8/3/04. However, no Form 1449 is of record as having been filed on the said date.

8. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

9. The amendment filed 2/6/04 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the incorporation by reference to parent applications in the first line of the specification, wherein the amendment filed 2/6/04 is not mentioned in the declaration. The Examiner notes that the amendment filed 9/15/06 is a further amendment of the first line of the specification, and it contains the said incorporation by reference to the parent applications.

Applicant is required to cancel the new matter in the reply to this Office Action.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 37-41 and 48-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the expression vector(s) recited in the instant claims.

The instant claims encompass an expression vector or a pair of vectors, including poxvirus vector(s) such as MVA, wherein the said vector(s) *comprise* a nucleotide sequence encoding (*i.e., comprising*) a *modified* 5T4 antigen, including human, or wherein the modified 5T4 antigen *comprises* a peptide epitope of 5T4 antigen, including one of SEQ ID NO: 5-17, and wherein the modification is any modification of any portion of any 5T4 antigen, including from any species, and wherein in the instance of SEQ ID NO: 5-17, undisclosed flanking amino acid sequences are present that are not in the 5T4 protein of origin from which the SEQ ID NO is a subsequence or an altered subsequence, and including for claims 37-41 wherein the modified 5T4 antigen is capable of inducing an anti-tumor immunotherapeutic response in a subject, including wherein the said response is a CTL or an antibody response, and including for claims 48-53 wherein an immune response is primed and boosted in a subject.

The specification discloses that human 5T4 is characterized by Myers *et al*, the sequence of which appears in GenBank at accession no. Z20983 and is set out as SEQ ID NO: 1 of the instant application (page 5 at lines 13-15). Evidentiary reference GenEmbl Accession No. Z209083 teaches the sequence of Accession no. Z29083, human 5T4 gene for 5T4 oncofetal antigen. It is noted by the Examiner that the elected species SEQ ID NO: 5 is a subsquence of the human 5T4 protein, and as such it is not modified. Therefore instant claim 41 encompasses an expression vector wherein the modified 5T4 antigen comprises a peptide sequence selected from SEQ ID NO: 5 or any of the other recited SEQ ID NO that are unaltered subsequences of human 5T4 protein flanked by undisclosed sequence that are not contiguous flanking sequence from human 5T4 protein.

The specification discloses that a modified 5T4 antigen is a polypeptide that has been truncated, extended or otherwise mutated such that it differs from naturally occurring 5T4. The specification discloses that 5T4 peptides may be mutated by amino acid insertion, deletion or substitution, may be any length, but are advantageously between 5-25 amino acid residues, and preferably between 6 and 15 amino acid residues. The specification discloses that the peptides are able to bind HLA molecules and to induce CTL responses against wild-type 5T4 in subjects, often more effectively than full length 5T4 (page 5 at lines 22-32). The specification further discloses that human 5T4 consists of SEQ ID NO: 1, mouse 5T4 consists of SEQ ID NO: 2 and canine 5T4 consists of SEQ ID NO: 3, and that the invention comprises species and allelic variations of 5T4, as well as fragments, preferably distinct epitopes, and variants thereof comprising amino acid insertions, deletions or substitutions that retain the antigenicity of 5T4 (page 5 at lines 12-20). The specification discloses that MVA vectors comprising nucleic acid molecules that correspond to the coding sequence of human or mouse 5T4 were effective in raising a high titre of antibodies when administered to mice (Example 9), and that in mouse tumor models, mice vaccinated with MVA-h5T4 or MVA-m5T4 were able to mount anti-tumor activity when challenged with a syngeneic tumor line expressing the human or mouse 5T4 protein with resulting tumor retardation or lowered tumor burden (Examples 3-8).

As to the issue of "*comprise and encodes*", the specification does not disclose wherein the vector(s) encode a nucleic acid sequence comprising one of SEQ ID NO: 5-17 with undisclosed flanking sequences, nor variants of altered subsequences of 5T4 proteins comprising undisclosed flanking sequences not in the protein of origin, nor species other than human, murine or canine.

The art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, *i.e.,* a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo *et al* at page 366, column 1 lines 1-10.) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends" , but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27). The minimum length for a peptide to be a T cell epitope for class II MHC is about 12 amino acid residues (Rammensee *et al* at page 181, column 2, first full paragraph).

In addition, the art recognizes that flanking sequences influence the processing and presentation of CTL epitopes (Eisenlohr *et al*, Shastri *et al*, Bergmann *et al*, Wang *et al*, Perkins *et al*, Theoboald *et al* and Gileadi *et al*) and that immunodominance can be affected by the context of the epitope within the protein molecule and that junctional neoepitopes can be created (Perkins *et al*) or that immunodominant epitopes can be completely silenced by contiguous sequences (Wang *et al*).

The specification provides no disclosure that modified 5T4 antigens encoded in the vector(s) of the claimed invention are immunogenic, either as CTL, Th or B cell epitopes. *In vivo* studies disclosed in the instant specification utilize whole unaltered human or murine 5T4 as enunciated supra. Celis *et al* teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Further, although *experimental* ranking schemes are available for predicting relative binding strengths of some HLA binding nonapeptides, and assays are available to test the binding of peptides to HLA, an undue amount of experimentation would be involved in determining peptides from the many possibilities that would be capable of binding to HLA, inducing a CTL response and producing a clinical endpoint. Celis *et al* teach that "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether peptides can function as effective CTL antigens." Ochoa-Garay *et al* teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide

hydrophobicity and stability can influence the *in vitro* induction of CTL responses" (especially page 279, last sentence and continuing onto page 280). Karin *et al* teach that amino acids in an MHC binding peptide that are not the amino acids which participate in MHC binding can have a profound effect on whether or not a peptide is immunogenic. Chaux *et al* (Int. J. Cancer 77 538-542, 1998) teach that it is unclear if peptides from tumor specific proteins possessing anchor residues for binding to class I MHC produce CTL responses in patients vaccinated with the said peptides. It would require undue experimentation to determine which of the trillions of modified 5T4 antigens encompassed by the claimed invention are immunogenic and which are not.

In addition, the specification provides no disclosure that the SEQ ID NO recited in instant claim 41 that were selected by prediction algorithm and shown to bind to HLA-A*0201 are immunogenic, *i.e.*, induce CTL, and can produce a clinical endpoint in inducing an anti-tumor immunotherapeutic response. Although the instant specification discloses that immunization with vector(s) encoding unmodified full-length human or murine 5T4 protein in mouse tumor models could produce a clinical response *in vivo*, there is no disclosure that the isolated SEQ ID NO can produce the clinical result, even if capable of inducing CTL.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1404-7 (Fed. Cir. 1997). In University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (*i.e.,* nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of

specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including an expression vector(s) comprising a nucleic acid sequence encoding a modified 5T4 antigen, said antigen that includes a polypeptide that has been truncated, extended or otherwise mutated, by amino acid insertion, deletion or substitution, such that it differs from any naturally occurring 5T4, variant or allele derived from any species. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

12. Claims 37-41 and 48-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification has not enabled the breadth of the claimed invention because the claims encompass an expression vector or a pair of vectors, including poxvirus vector(s) such as MVA, wherein the said vector(s) *comprise* a nucleotide sequence encoding (*i.e., comprising*) a *modified* 5T4 antigen, including human, or wherein the modified 5T4 antigen *comprises* a peptide epitope of 5T4 antigen, including one of SEQ ID NO: 5-17, and wherein the modification is any modification of any portion of any 5T4 antigen, including from any species, including wherein the modified 5T4 antigen is capable of inducing an anti-tumor immunotherapeutic response in a subject, including wherein the said response is a CTL or antibody response, an including wherein an immune resonse is primed and boosted in a subject. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed expression vector(s) can be made and/or used.

The specification discloses that human 5T4 is characterized by Myers *et al*, the sequence of which appears in GenBank at accession no. Z20983 and is set out as SEQ ID NO: 1 of the instant application (page 5 at lines 13-15). Evidentiary reference GenEmbl Accession No. Z209083 teaches the sequence of Accession no. Z29083, human 5T4 gene for 5T4 oncofetal antigen. It is noted by the Examiner that the elected species SEQ ID NO: 5 is a subsquence of the human 5T4 protein, and as such it is not modified. Therefore instant claim 41 encompasses an expression vector wherein the modified 5T4 antigen comprises a peptide sequence selected from SEQ ID NO: 5 or any of the other recited SEQ ID NO that are unaltered subsequences of human 5T4 protein flanked by undisclosed sequence that are not contiguous flanking sequence from human 5T4 protein.

The specification discloses that a modified 5T4 antigen is a polypeptide that has been truncated, extended or otherwise mutated such that it differs from naturally occurring 5T4. The specification discloses that 5T4 peptides may be mutated by amino acid insertion, deletion or substitution, may be any length, but are advantageously between 5-25 amino acid residues, and preferably between 6 and 15 amino acid residues. The specification discloses that the peptides are able to bind HLA molecules and to induce CTL responses against wild-type 5T4 in subjects, often more effectively than full length 5T4 (page 5 at lines 22-32). The specification further discloses that human 5T4 consists of SEQ ID NO: 1, mouse 5T4 consists of SEQ ID NO: 2 and canine 5T4 consists of SEQ ID NO: 3, and that the invention comprises species and allelic variations of 5T4, as well as fragments, preferably distinct epitopes, and variants thereof comprising amino acid insertions, deletions or substitutions that retain the antigenicity of 5T4 (page 5 at lines 12-20). The specification discloses that MVA vectors comprising nucleic acid molecules that correspond to the coding sequence of human or mouse 5T4 were effective in raising a high titre of antibodies when administered to mice (Example 9), and that in mouse tumor models, mice vaccinated with MVA-h5T4 or MVA-m5T4 were able to mount anti-tumor activity when challenged with a syngeneic tumor line expressing the human or mouse 5T4 protein with resulting tumor retardation or lowered tumor burden (Examples 3-8).

As to the issue of "*comprise and encodes*", the specification does not disclose wherein the vector(s) encode a nucleic acid sequence comprising one of SEQ ID NO: 5-17 with undisclosed flanking sequences, nor variants of altered subsequences of 5T4 proteins comprising undisclosed flanking sequences not in the protein of origin, nor species other than human, murine or canine.

The art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, *i.e.,* a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo *et al* at page 366, column 1 lines 1-10.) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends" , but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27). The minimum length for a peptide to be a T cell epitope for

class II MHC is about 12 amino acid residues (Rammensee *et al* at page 181, column 2, first full paragraph).

In addition, the art recognizes that flanking sequences influence the processing and presentation of CTL epitopes (Eisenlohr *et al*, Shastri *et al*, Bergmann *et al*, Wang *et al*, Perkins *et al*, Theoboald *et al*and Gileadi *et al*) and that immunodominance can be affected by the context of the epitope within the protein molecule and that junctional neoepitopes can be created (Perkins *et al*) or that immunodominant epitopes can be completely silenced by contiguous sequences (Wang *et al*).

The specification provides no disclosure that modified 5T4 antigens encoded in the vector(s) of the claimed invention are immunogenic, either as CTL, Th or B cell epitopes. *In vivo* studies disclosed in the instant specification utilize whole unaltered human or murine 5T4 as enunciated supra. Celis *et al* teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Further, although *experimental* ranking schemes are available for predicting relative binding strengths of some HLA binding nonapeptides, and assays are available to test the binding of peptides to HLA, an undue amount of experimentation would be involved in determining peptides from the many possibilities that would be capable of binding to HLA, inducing a CTL response and producing a clinical endpoint. Celis *et al* teach that "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether peptides can function as effective CTL antigens." Ochoa-Garay *et al* teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the *in vitro* induction of CTL responses" (especially page 279, last sentence and continuing onto page 280). Karin *et al* teach that amino acids in an MHC binding peptide that are not the amino acids which participate in MHC binding can have a profound effect on whether or not a peptide is immunogenic. Chaux *et al* (Int. J. Cancer 77 538-542, 1998) teach that it is unclear if peptides from tumor specific proteins possessing anchor residues for binding to class I MHC produce CTL responses in patients vaccinated with the said peptides. It would require undue experimentation to determine which of the trillions of modified 5T4 antigens encompassed by the claimed invention are immunogenic and which are not.

In addition, the specification provides no disclosure that the SEQ ID NO recited in instant claim 41 that were selected by prediction algorithm and shown to bind to HLA-A*0201 are immunogenic, *i.e.*, induce CTL, and can produce a clinical endpoint in inducing an anti-tumor immunotherapeutic response. Although the instant specification discloses that immunization with vector(s) encoding full-length unmodified human or murine 5T4 protein in mouse tumor models could produce a clinical response *in vivo*,

there is no disclosure that the isolated SEQ ID NO can produce the clinical result, even if capable of inducing CTL.

Accordingly, there is a high level of unpredictability in designing/selecting longer sequences or modified sequences that would be processed, still maintain binding function, elicit a CTL, Th or antibody response, and produce a clinical endpoint in inducing an anti-tumor immunotherapeutic response in a subject.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

13. No claim is allowed.

14. The references crossed out in the Form 1449 filed 8/23/99 have not been considered because they can't be located in the parent application Serial No. 09/533,798. They will be considered in the next Office Action. It would expedite prosecution if Applicant would send in copies of references.

15. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
September 22, 2006

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No. 10/774,176	Carroll et al.	
	Examiner Marianne DiBrino	Art Unit 1644	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The sequence submission filed 8/2/04 does not contain a statement that the content of the paper and CRF copies are the same, and where applicable, included no new matter.

Applicant Must Provide:

☒ A~~n initial or~~ substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ A~~n initial or~~ substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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